Tuberculosis: Past, Present and Future

Satellite Conference
Friday, April 16, 2004
2:00-4:00 p.m. (Central Time)

Produced by the Alabama Department of Public Health
Video Communications Division

Faculty

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Objectives

1. **Discuss one aspect of the relationship of bovine tuberculosis and European vampire legends.**
2. **Explain two ways the northern European concept of the hereditary nature of tuberculosis influenced the arts and attitudes about how the disease was spread.**

Objectives

3. **Explain two ways the influence of tuberculosis on literature and the performing arts as they expressed early theories about the nature of the disease and the devastation it was causing.**
4. **Describe one way the paintings of Rembrandt as an early record of the effects of this disease in people.**
5. **Describe how two cultural beliefs emerged from observation of the ravages of TB and influenced the way TB patients were handled.**

Tuberculosis, Vampires, and Mummies

An interrupted history of man, cows and the arts

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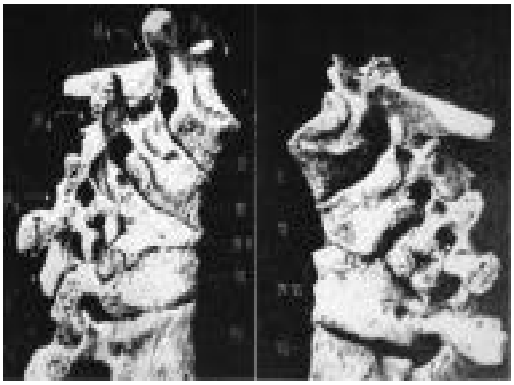
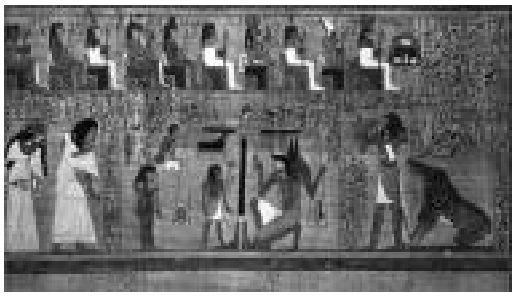
TB Deaths

Cardinal Richelieu
Alexander Pope
Luigi Boccherini
Amedeo Modigliani
Johann von Goethe
Sir Walter Scott
Fyodor Dostoyevsky
Eleanor Roosevelt
Robert Louis Stevenson
Doc Holiday
Igor Stravinski
D H Lawrence
Eugene O'Neill
Freidrich Schiller
Franz Kafka
Tom Fogerty
Jimmie Rogers





Hippocrates

- Recognized phthsis
- Pulmonary vs Spinal
- Confused with empyema
- Described rales, rubs, succusion
- Used “tubercle” for any nodule
- No autopsies
- Hereditary

Galen (c129 - c200)

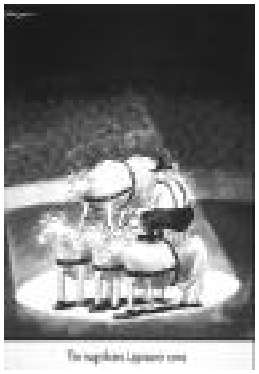
- 500 books (80 survive)
- Animal dissection
- Sanguine, phlegmatic, melancholic, and choleric humors
- Pulmonary phthsis well described
- Contagious
- Rest, milk
- Specific potions (theriac)

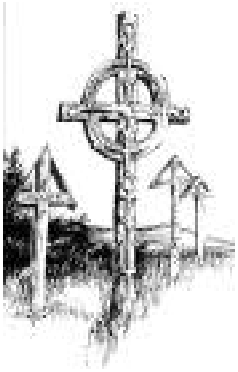
Lamia (lamiae)

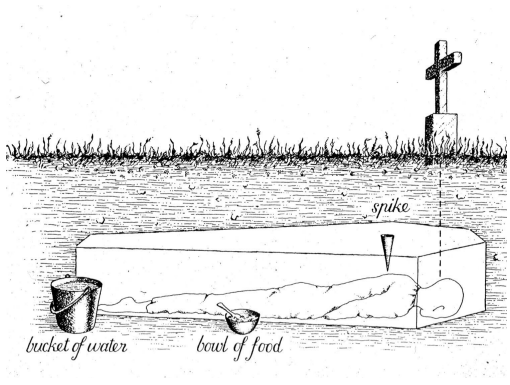
The Golden Ass **-- Apuleius**

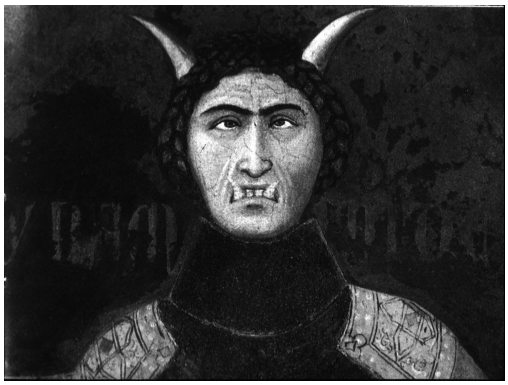
Vrykolakas

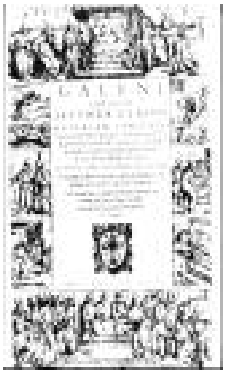
- **Constantine**
- **Fall of Rome**
- **Eastern Orthodox Church supported concept of vrykolakas**
- **Holy Roman Empire suppressed progress -**
  Galen's ideas maintained











MacDuff: What's the disease he means? Malcolm: It's called the evil;

A most miraculous work in this good King which often, since my here remain in England, I have seen him do. How he solicits heaven, Himself best knows; but strangely visited people, All swol'n and ulcerous, pitiful to the eye, The mere dispair of surgery, he cures, Hanging a golden stamp about their necks Put on with holy prayers; and 'tis spoken, To the succeeding royalty he leaves The healing benediction. -- *Macbeth* act 4, scene 3

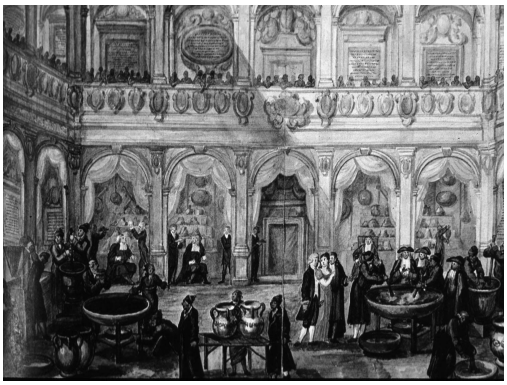
Malleus Maleficarum

-- Pope Innocent VIII (1486)

16th and 17th Centuries

- **Vesalius - anatomy**
- **Frascotorious - foamites**
- **Consumption 20 - 25% of all deaths**

- **Dissertario Historica Philosophica de Masticatione Mortuorum (1679)**
- **De Masticatione Mortuorum in Tumulis Liber (1728)**
- **Disertatio Physica Cadaveribus Sanguisugis (1732)**



Hamlet: How long will a man lie i' the earth ere he rot?

1st clown: I' faith, if a' be not rotten before a' die,…a' will last you some eight year or nine year. A tanner will last you nine year.

--*Hamlet* act 5, scene 1

"Pore Jud is Daid"

He looks like he's asleep,
it's a shame that he won't keep,
but it's summer and we're runnin'
out o' ice.

Oklahoma!

Detecting a Vampire (the grave)

- **Disturbed earth**
- **Fallen tombstone**
- **Footprints**
- **Dogs bark**
- **Horses shy**

Detecting a Vampire (the corpse)

- **Open eyes**
- **Ruddy complexion**
- **Nail growth**
- **Lack of decomposition**
- **Blood around mouth**
- **Shrieking and bleeding when staked**

Destroying A Vampire

- **Burning**
- **Staking**
- **Removing head or heart**
- **Help from sun, garlic, and religious artifacts**

"Documented" Vampires

- **Peter Plogowitz - Hungary (1725)**
- **Arnold Paole - Serbia (1726)**
- **Johann Fluckinger (1732)**
  Visum et Repertum

Trait surles Revenants en Corps, las Excommunies, les Oupires ou Vampires, Broueolaques de Hongrie, de Moravie, etc.

--Dom Calmet (1746)

The health of the human body shall not be harmed or imperiled by objects remaining after death of a person dying of phthsis.

Republic of Lucca - 1699

18th Century

- **Industrial revolution**
- **Consumption 25-33% of all deaths**
- **Continued disagreement on contagion**

"It was the fashion to suffer from the lungs; everybody was consumptive, poets especially; it was good form to spit blood after each emotion and to die before the age of thirty."

--Alexander Dumas

TB in Fiction

Marguerite Gautier	**La Dame au Camelias**
Violetta	**La Traviata**
Mimi	**La Boheme**
Leonora	**La Favorata**
Little Blossom	**David Copperfield**
Smike	**Nicholas Nickleby**
Fantine	**Les Miserables**

I look pale . . . I should like to die of consumption - because the ladies would say, "Look at poor Byron, how interesting he looks in dying".

--Lord Byron

But first, on earth as vampire sent,
Thy corpse shall from it's tomb be rent;
Then ghastly haunt thy native place,
And suck the blood from all thy race

--Lord Byron *The Giaour*

I saw pale kings, and princes too
Pale warriors, death pale were they all,
They cried "La Belle Dame sans Merci
Hath thee in thrall!"

John Keats (1819)

This consumption is a disease particularly fond of people who write good verses such as you have done . . . I think you would do well to pass the winter in Italy as long as you find Pisa agreeable.

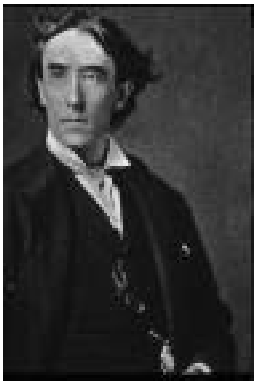
-- P B Shelley

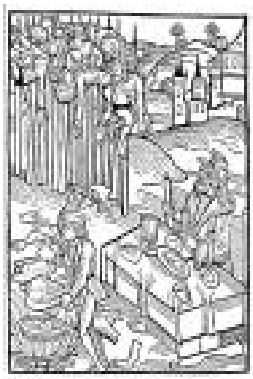
"Those brutal Italians have nearly finished their monstrous business. They have burned all the furniture - and are now scraping the walls - making new windows - new doors - and even a new floor."

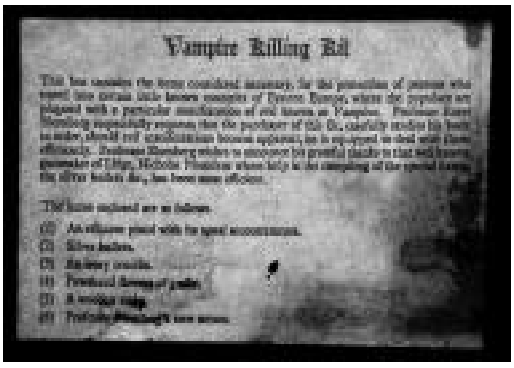
Joseph Severin, Rome, 1821

By now, thy youngest, dearest one has perished - The nursling of thy widowhood, who grew, like a pale flower by some sad maiden cherished,
And fed with true-love tears, instead of dew, most musical of mourners, weep anew!
Thy extreme hope, the loveliest and the last, the bloom, whose petals nipped before they blew died on the promise of the fruit, is waste; The broken lily lies - the storm is overpast.

Percy Bysshe Shelley --*Adonais*






Vampire Killing Kit

“Is that man, brought into the arena at the moment of death, like a dying gladiator, to delight the public with his convulsion? Or is it one risen from the dead, a vampire with a violin, who if not the blood out of our hearts, sucks the gold out of our pockets?”

--Heine

Rene Lannec (1781-1824)

- **Stethoscope**
- **Autopsies**
- **Unified forms of consumption**
- **Called disease “Tuberculosis”**
- **Died of TB**

"Is it possible that genius is only scrofula?"

-- Elizabeth Barrett Browning

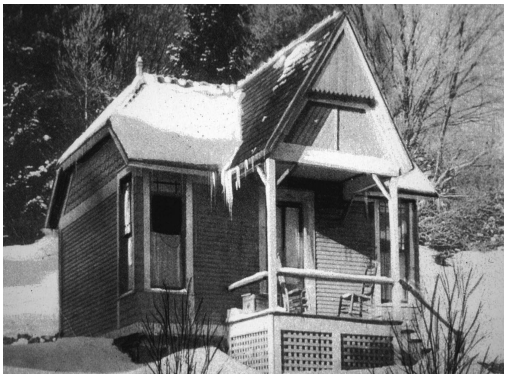
New World microbes. This 908-year-old mummy had TB DNA.

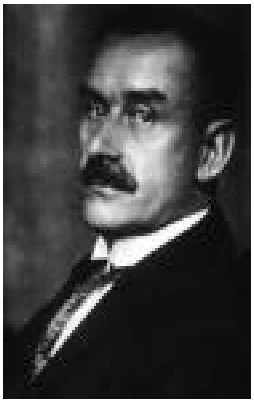
Historical U.S. Vampires

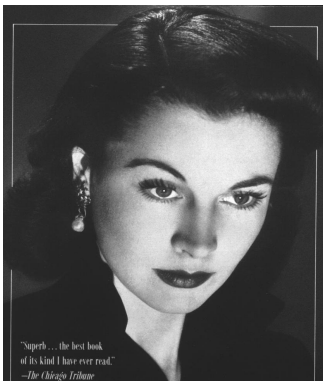
Stuckley (1770) Rural, RI, F, consumption
Burton (1790) Manchester, VT, F, consumption

Ransom (1817) Rural, VT, M, consumption
Corwin (1829) Woodstock, VT, M consumption
Ray (1854) Jewett City, CT, M*, consumption
Rose (1874) Peacedale, RI, F, consumption
Unknown (1875) Chicago, IL, F, consumption
Brown (1892) Exeter, RI, F*, consumption

***3 vampires**







Oil and Blood

In tombs of gold and lapis lazuli
Bodies of holy men and women exude
Miraculous oil, odour of violet

But under heavy loads of trampled clay
Lie bodies of vampires full of blood;
Their shrouds are bloody and their lips are wet

- - W.B. Yeats

TB 2004: Updated Treatment Guidelines, Diagnostics and Future Vaccine Development

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Overview/Summary (1)

- Health professionals must "Think TB"
- The Public Health Department is responsible for oversight and successful completion of TB therapy in patients
- TB treatment:
  - Overview
  - Updated guidelines on dose count
  - Hospitalization issues and the TB patient
  - Assessing high-risk-of-failure patients
  - New regimen options

Overview/Summary (2)

- Issues in HIV-related TB:
  - Rifamycin interactions with anti-retrovirals
  - Paradoxical reactions or "IRIS" (Immune Reconstitution Inflammatory Syndrome)
  - Thrice-weekly therapy needed in advanced HIV
- New method of testing for latent infection: Quantiferon assay
- Future vaccine developments

"Think TB"

- Or the diagnosis will be delayed or missed, resulting in:
  - ***increased*** patient morbidity
  - ***further*** spread of TB into the community
  - resulting in ***further*** burden on public health care personnel and resources to identify and screen contacts and treat ***further*** cases of both active disease and latent infection
  - Propagation of TB as an active issue in the community (e.g., contradicts CDC's "TB Elimination" goal)

"Think TB"

- If the disease is ***not*** thought of, the diagnosis will not be readily made
- If the disease ***is*** thought of, a ready and cheap test, the AFB smear, can make a quick diagnosis in the majority of cases, and identify those patients at greatest risk of spreading the disease to others

Illustrative Case

- 32 year old woman with a history of mental disorder, visits local ER in May 2002 for productive cough of several weeks, diagnosed with "bronchitis", given antibiotics and sent home
- In the following several months, she visits several different ER's and primary medicine clinics for respiratory symptoms and diagnosed repeatedly with "bronchitis" or "walking pneumonia"

Case (continued)

- The patient was given an outpatient pulmonary referral and did not follow-up
- In October 2002 (6 months from the onset of symptoms and seeking health care) an ER physician orders an AFB smear
  - Result comes to the health department "smear positive numerous"
- CXR with bilateral upper lobe cavitary infiltrates (classic for TB)

Case (continued)

- In this example, both the patient and health system factors resulted in great delay in diagnosis
  - As health care workers, we should be as "proactive" as we can in diagnosis and follow-up, especially when recognizing patients with factors which may hinder their own ability to address their problem

"Think TB"

- Some health professionals: "*I thought TB was gone now*?"
  - Reflects successful decades of ongoing public health efforts to contain the disease and identify those at greatest risk
  - But danger comes with being lulled into complacency, TB can always rebound (e.g. NYC in 1980's)
    - Closely linked to funding, which is often linked to visible (active) TB problem
- "Eternal vigilance"

Role of the Health Department

- The Health Department is responsible for oversight and successful completion of TB therapy in patients
- Successful early diagnosis is usually relied on by health care in the community (clinics, hospitals) but once the diagnosis of TB is made or suspected, immediate referral to the health department should be done (including direct contact of HD workers) to evaluate, institute care and follow patients

Role of the Health Department

- TB is a required reportable disease to the health department
- Notifications required by: physicians, hospitals, laboratories, pharmacies (when filling prescription for > 1 TB drug)
- Free medications and services provided for all TB-related care

Role of the Health Department

- Well established protocols and guidelines for treating and following patients in order to maximize successful outcome and minimize development of TB drug resistance
- DOT – Directly Observed Therapy is a backbone of successful treatment outcome and is performed by TB nurses and Disease Intervention Specialists (DIS)

Role of the Health Department

- The Health department does not replace the primary physician's role, only oversees the "labor-intensive specifics" that are necessary in order to successfully cure and educate the TB patient and investigate other susceptible individuals in their surroundings
- TB workers often discover previously unnamed contacts by getting to know the patient and their environment over time

TB Treatment

- Short Course Chemotherapy (SCC)
- Total 6 months therapy
- ***Intensive*** Phase: 2 months with 4 drugs: isoniazid (INH), rifampin, pyrazinamide (PZA), ethambutol
- ***Continuation*** Phase: 4 months with 2 drugs: INH, rifampin

Treatment

- Medications are given ***daily*** for the first two weeks
- The remainder of therapy is given twice weekly (adjusted doses)
- All doses are directly observed by a TB health care worker
- Decade of studies regarding duration and intermittent dosing

Treatment: Hospitalization

- No need to hospitalize TB patient unless very ill
  - Initial 2 weeks of daily therapy serves to educate the patient and build a relationship with the health department staff, but does not influence efficacy

Treatment: Hospitalization

- In a hospitalized TB patient, no need to keep as an inpatient until the smear is negative
  - Threat of infecting others drastically reduced once TB therapy begins
  - Social and housing problems often a disposition issue

Treatment

- ***Short course*** (6 month) therapy requires:
  - both INH and rifampin used throughout
  - PZA is used for the first 2 months
  - patient's TB strain is susceptible to all drugs being used
- Smear conversion, immune status, CXR improvement are other factors

Treatment

- Sputum smears and cultures are followed weekly until conversion to negative, then monthly until completion of therapy
- Delayed conversion is present if patient is still smear positive at 2-3 months into therapy
- This is a warning against the "fall and rise" phenomenon which may indicate impending treatment failure and development of acquired drug resistance

Treatment

- In this case, 2 totally new TB drugs must be *added* to the patient's regimen (preferably one being an injectable: like streptomycin)

  TB adage: "Never add a single drug to a failing regimen"
- A repeat drug sensitivity test on a recent culture should be done to look for new resistance
- If available, serum levels of TB drugs should be checked to insure adequate absorption

New Issues in Treatment

- Emphasis should be on completing the total number of doses (52 for a 6 month regimen) and not just the duration of therapy
  - Dose count should be performed before closing out the patient's case

New Issues in Treatment

- Rifapentine, a long acting rifamycin, in certain *carefully selected* cases can be used together with INH in the *continuation* phase as once a week therapy
- Exclusion criteria: HIV co-infection, cavitation on CXR and delayed sputum conversion
  - high risk of failure, acquired rifamycin resistance and relapse

New Issues in Treatment: Fluoroquinolones

- Initially found to be effective against TB incidentally and used as second line drugs, but now found increasingly to be very potent and rapidly bactericidal and have an evolving more front-line role
- Moxifloxacin recently found to be as rapidly sterilizing as INH
  - moxi > levaflox > oflox > cipro

Rx of LTBI (Latent TB Infection)

- Standard: INH x 6-9 months
- Alternate: Rifampin daily x 4 months
- Others: Options available depending on the context (e.g. Contact to MDR case)
  - Recent Rif/PZA controversy (2 month regimen): unacceptably high rates of severe liver injury and death
- DO*P*T given in some high risk situations
  - e.g. children, HIV+

Special Situations: HIV-TB

- HIV infection is the greatest risk factor for development of active TB (10% per year with a positive PPD skin test vs. 10% lifetime in HIV-uninfected)
- Globally, TB is the #1 killer of HIV-infected patients
- Risk of death during TB treatment and relapse following cure is higher in HIV patients

Special Situations: HIV-TB

- Co-administration of TB drugs and HIV drugs presents unique drug interaction challenges
- The " #1" backbone TB drug, rifampin, significantly interacts with the backbones of HIV therapy, protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI)

Special Situations: HIV-TB

- Treatment strategies include:
  - Substituting rifabutin for rifampin, with dose adjustments to account for drug interactions
  - Using efavirenz (Sustiva), an NNRTI which can be used with rifampin*
  - Designing a TB regimen without rifampin (or continuation phase)
  - Designing a HIV regimen without a PI or NNRTI
  - Delaying HIV therapy until TB treatment is completed

Special Situations: HIV-TB

- None of these strategies is perfect and each has potential pitfalls
- Overall, the combined management of both diseases is complex and requires management and co-ordination between TB and HIV health care staff

Other Issues In TB-HIV

- "Paradoxical reactions" common during therapy, especially when receiving rx for both diseases
  - Newly named "Immune Reconstitution Inflammatory Syndrome" (IRIS)
  - As diseases are treated, patient's immune system recovers and mounts inflammatory reactions in lungs, lymph nodes or elsewhere, showing apparent worsening of disease
  - In severe cases, drugs may need to be held or steroids given

Other Issues in TB-HIV

- In April 2003, CDC (MMWR) published reports of HIV-TB patients failing therapy during continuation phase and developing rifampin mono-resistant disease
- Found to occur in advanced HIV patients with CD4 counts less than 100
- Guidelines changed to use three-times weekly dosing in all HIV-TB patients unless CD4 count known to be > 100

New Methods of Detecting Latent TB Infection: QuantiFERON-TB Assay

- PPD (Purified Protein Derivative) and other skin tests used for over 50 years to assess exposure and infection by tuberculosis
- Limitations of PPD include:
  - Cross-reaction with other mycobacteria
  - Cannot distinguish TB from BCG vaccination

New Methods of Detecting Latent TB Infection: QuantiFERON-TB Assay

- Limitations of PPD include:
  - Lack of sensitivity in some patients
  - Requirement to have patient return in 48-72 hours
  - Subject to reader bias of reaction

QuantiFERON-TB

- Attempts are being made to use modern molecular methods to detect TB infection more accurately
- QF is an attempt to detect if *specific* T cells are present in patient which have "memory" of TB infection

QuantiFERON-Method Overview

- Four whole blood samples from patient are incubated and stimulated (within 12 hours): TB proteins, MAC, mitogen, nil (control)
- If T cells are present, they produce gamma-interferon (*y*-INF)
- Plasma samples assayed for *y*-INF and % difference for TB and MAC determined
- Based on a patient risk group (cutoff), results used to determine probability of TB infection

QuantiFERON-Limitations

- Initial studies showed .35-.68 concordance (*k*) (different populations)
- CDC suggests use for those at low risk of LTBI (e.g. pre-employment, military)
- Also for foreign born, health workers, homeless, but confirm +QF test with PPD
- Exclusions: people < 17 or > 50, recent contacts, TB suspects, HIV+ or other immune deficiency, prior BCG, pregnancy
- Technical aspects, cost

QuantiFERON-Future

- Further studies in different populations to see where QF could be most applicable
- Assay could potentially be refined using other antigens to stimulate T cells which are more specific to M. *tuberculosis* (e.g. ESAT-6)

TB Vaccine

- History use of BCG
  - Limitations
- Research to improve
  - Challenge because even true infection is not always protective (*i.e.* re-infection documented even in normal hosts)
  - Work on finding protective Ag's and then enhancing or boosting IR to them with adjuvants (IL-2, g inf, IL-12)
- Current vaccine status (recent NIAID) report

Upcoming Programs

Implementing Self-Management Education: Successes & Challenges in Arthritis
Tuesday, April 20, 2004
12:00-3:00 p.m. (Central Time)

What to Expect From Your Local Hospital's Response to Emergency Events
Thursday, April 22, 2004
12:00-1:30 p.m. (Central Time)

Upcoming Programs

Bridging Traditional Environmental Health and Health Promotion
Wednesday, May 5, 2004
2:00-3:00 p.m. (Eastern Time)

Transforming Vision to Reality: Potential Power of Partnership
Thursday, May 6, 2004
2:00-3:00 p.m. (Eastern Time)

Upcoming Programs

Principles for Effective Communication of Health Risks in High Concern, High Stress Situations
Friday, May 7, 2004
2:00-3:00 p.m. (Eastern Time)

For a complete listing of all programs, visit our website:
www.adph.org/alphtn